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Mycosis Fungoides: Clinical Course and Cellular Abnormalities

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Mycosis fungoides is a lymphoma that appears to begin in skin. Although variable in its clinical course, it tends to affect middle-aged people, is present for a median of 4 yr before diagnosis, and generally results in death of the patient 4 to 5 yr after diagnosis. Cutaneous tumors and palpably enlarged lymph nodes are associated with shortened survival, and each of these frequently is accompanied by extracutaneous dissemination of the disease. The malignant cells are T lymphocytes with highly infolded nuclei, and they frequently express a helper cell function. Their chromosome complement has been found to be abnormal in karyotyping studies, and measurement of the amount of DNA by cytophotometry may permit diagnosis of the disease before the histological characteristics are detectable by light microscopy.

Mycosis fungoides (MF) is a disease whose complete manifestations have allowed ready diagnosis by clinicians, have engendered confusion and disagreement among histologists, and have provided, during the 1970s, a growth industry for immunologists. The disease was described 175 yr ago by Jean Louis Alibert, who was born in 1768 in Villefranche, a small town in the south of France. After being trained as a priest, he returned home to teach, but the French Revolution was hard on priests and the new laws forced the then 24-yr-old Alibert to change his profession. Because he could no longer serve God, he followed the next most honorable calling and became instead the founder of French dermatology. He described many cutaneous afflictions, including lupus vulgaris, keloids, cutis laxa, and, in 1806, what is now called mycosis fungoides. The 1st patient was a 56-yr-old man with a scaly eruption that progressed to painless, skin-colored nodules. "Later," he noted, "the skin which covers the nodules opens, and each tubercle becomes a fetid ulcer. As decomposition progresses, these tubercles take on a greenish-black color or a very dark violaceous tint. One can picture them as fruits rotting on the stem that bears them. By comparison even with the ravages of untreated tertiary syphilis these lesions are almost always more horrible." "After some months," he went on, "the patients fall little by little into a state of emaciation that weakens them to the extreme [and] they end up by succumbing or leading a miserable life for many years" [1].

This description covers the central features of the disease as it is still seen. It starts as a nonspecific, scaly dermatitis, and infiltrated lesions develop gradually. These become frank nodules and grow to form tumors that ulcerate and destroy normal structures. Eventually, the patient becomes cachectic and dies, although there is great variability in the extent to which the disease progresses and in the time taken to reach the final stage.

This review focuses on some of the data published in the past decade regarding (a) the clinical course of the disease and its response to treatment, (b) morphological cellular abnormalities in the skin, lymph nodes, blood, and other tissues of MF patients, and (c) studies on the functioning of the abnormal cells. The relevance of this discussion to the theme of this volume lies in a consideration of the likelihood that the behavior of the abnormal cells in these patients reflects at least in some aspects that of their normal counterparts and that this reflection may help us to understand normal cells better.

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Abbreviations:
MF: mycosis fungoides
NCI: nuclear contour index

CLINICAL FINDINGS

Mycosis fungoides has been considered a capricious disease with an extremely variable clinical course. Undoubtedly, this partially valid characterization has been due to a lack of reports of large series of MF patients. Within the past decade, data on 5 large groups of patients have been collected and reported in the U.S., and we now can be much more confident in speaking about the prognosis of these patients [2–6]. Most commonly, the disease develops in middle-aged people; a few are so unlucky as to have it before 20 yr of age, and a few do not get lesions until over 70 yr of age. In perhaps 85% of patients, the disease begins as a poorly defined, patchy, erythematous, and scaly eruption. In some patients these nonspecific changes persist for decades, but the median period between appearance of lesions and diagnosis by biopsy is approximately 4 yr [2,3]. The nature of the lesions during the period of nonspecific changes is variable and poorly defined. Often the eruption is diagnosed as eczema or psoriasis, but generally in retrospect the clinical appearance in such cases was not completely typical of these diseases. It is doubtful that completely typical psoriasis becomes MF, although by chance the two might afflict the same patient occasionally. There are intriguing anecdotal reports of patients whose disease began unquestionably as contact dermatitis and then showed chronic changes and eventually became frank MF. Cohen and associates [3] and subsequently Greene and co-workers [7] pointed out that patients with MF are more likely to be employed in manufacturing, in construction, or especially in the petrochemical industry where they may have been exposed to more than the usual contact irritants, allergens, and toxic materials. There is also a more specific pre-MF condition—parapsoriasis en plaques. This condition is characterized by variably sized areas of dull pink macules, sometimes with minimal scaling. These tend to spread over periods of months to years. They sometimes change location, i.e., disappear in one area and develop in another. Sometimes they become poikilodermatous with atrophy, dyschromia, and telangiectasia. In small series of patients with this condition, 14 to 46% were found later to have MF [8,9]. Methods for accurately predicting which patient will have a benign course and which a more malignant one would be useful because the usual light microscopic examination of affected tissue cannot differentiate the fatal from the nonfatal form of the disease. Yet another variant of what may be pre-MF was described a decade ago under the name of lymphomatoid papulosis [10]. Patients with this condition have red papules that may become pustular, ulcerate, heal in about 1 mo, and leave scars. The notable feature is spontaneous healing despite what may appear to be a highly malignant infiltrate. Although the condition was originally described as benign, some patients have been reported later to have frank MF [11], and we have seen several patients in San Francisco who have had coexisting typical lesions of MF and lymphomatoid papulosis.

Once the clinician and the pathologist have agreed on the

diagnosis of MF, the median survival is 3 to 5 yr [2,3]. Probably the most significant factors enabling prediction of survival after diagnosis are the types of lesions present on the skin and the presence or absence of palpably enlarged superficial lymph nodes. Tumors (as opposed to flatter lesions) or palpably enlarged lymph nodes are associated with markedly shortened survival if present at the time of diagnosis; they also may develop later. A median survival rate of approximately 2 yr after the development of cutaneous tumors has been found in several series over several decades and appears not to have been changed appreciably by modern therapy. If one evaluates only lymph nodes accessible to palpation, one obviously cannot determine the size of many nodes. The value of bipedal lymphangiography in classifying the stage of MF is in dispute [12,13], but it is apparent that peripheral nodes are involved earlier and to a greater degree than more proximal nodes. This pattern of invasion has been elucidated further by findings at staging laparotomies in a small number of patients [14,15] and at autopsy in a large number of patients [16]. These studies have helped physicians explain the poor survival rate noted in patients with cutaneous tumors or palpably enlarged lymph nodes. Patients with tumors on their skin generally have extracutaneous disease, and patients with lymph node MF found at autopsy all had MF in other tissues besides skin and lymph nodes. Hence it appears that the "barrier" to dissemination is in skin, not lymph nodes. Once malignant cells have invaded the lymph nodes, they have also invaded other tissues. The lungs, spleen, and liver are the other organs most often invaded. Invasion of bone marrow occurs only infrequently, but essentially all tissues may be invaded [2].

HISTOLOGY

With light microscopy the diagnosis of MF relies on the overall pattern of cellular infiltration as well as on the cytologic abnormalities of individual cells. The pattern is that of an infiltration of the upper dermis and, of especial note, of the epidermis. The cells infiltrating the epidermis may do so singly, but more characteristically they form small clusters, termed Pautrier microabscesses, in the lower epidermis. These microabscesses, although not pathognomonic of MF, are quite characteristic of the disease, and pathologists emphasize their presence in making the diagnosis. The cells in the epidermis are mononuclear and fairly homogeneous, whereas the infiltrate in the upper dermis is more heterogeneous and consists not only of mononuclear cells but also of inflammatory cells, including polymorphonuclear leukocytes, eosinophils, and plasma cells. The mononuclear cells may vary in size and regularity, but some of them have a distinctive appearance, with a large hyperchromatic nucleus; it has been assumed that it is the latter type of cells that are malignant. When tumors develop, the pleomorphic character of the infiltrate diminishes, and the inflammatory infiltrate with a few malignant cells seen in the initial skin biopsy sample is replaced by the more abundant population of malignant-appearing mononuclear cells seen at autopsy [16]. It is cells with this appearance that invade extracutaneous sites. They infiltrate diffusely rather than in large nodules so that a generally normal parenchymal architecture is preserved. Although in the past systemic spread of MF was interpreted clinically and histologically as conversion to a more classic form of lymphoma such as Hodgkin's disease [17], the current interpretation is that MF remains a unique disease whether in the skin or at extracutaneous sites [16].

ELECTRON MICROSCOPY

When investigation of the disease was limited to macroscopic and light microscopic observations, the nosologic uniqueness of MF remained in question. The observation that began what might be considered the current era of investigation into MF was the electron microscopic discovery by Lutzner and Jordan [18] of a previously undescribed type of cell in the blood of patients with what is now accepted by most to be the leukemic

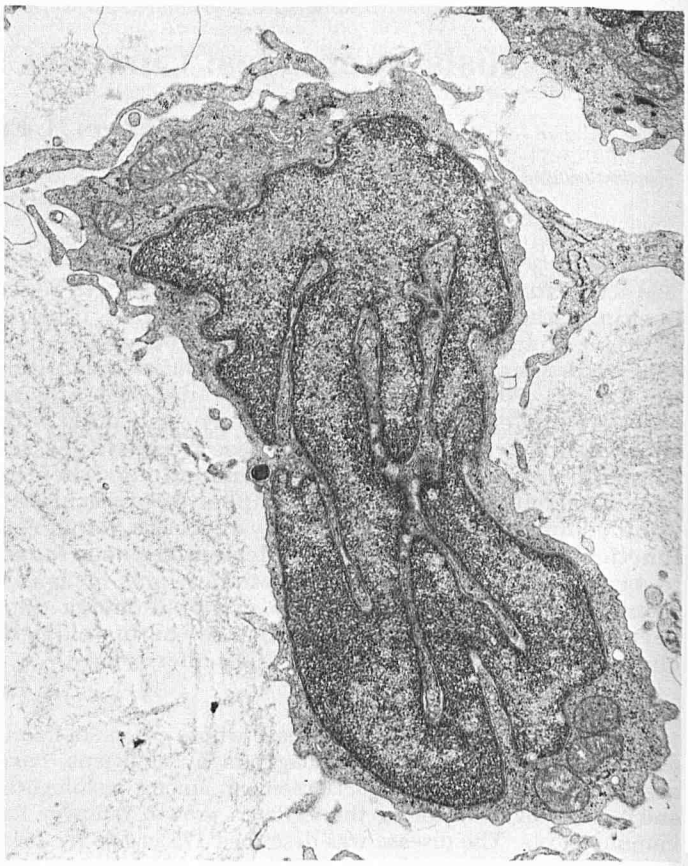

FIG 1. Electron microscopic appearance of cell from the skin of a patient with mycosis fungoides. The nuclear contour index of this cell is 13 (photograph courtesy of Scott McNutt, M.D.).

phase or variant of MF, the Sézary syndrome. This cell has a large, deeply infolded nucleus with peripheral condensation of the electron-opaque chromatin. Subsequently, Lutzner, Hobbs, and Horvath [19] found similar cells in the skin lesions of patients with Sézary syndrome and with MF. The specificity of this cell has been questioned because the original investigators, as well as others [20], found morphologically similar cells in patients with conditions unrelated to MF (e.g., lichen planus). Furthermore, 5 to 10% of peripheral blood leukocytes incubated for 72 hr with phytohemagglutinin show cerebriform nuclei resembling those in patients with Sézary syndrome [21]. Nonetheless, most pathologists still believe that these cerebriform cells are characteristic of MF, and they appear to be present in large numbers only in this disease. Sometimes they are seen in lymph nodes that by light microscopy show only the benign changes of dermatopathic lymphadenopathy; their presence suggests that routine light microscopic examination "underdiagnoses" lymph node invasion and this may explain the known bad prognosis of palpably enlarged lymph nodes even when the diagnosis is benign by routine examination. The confusion regarding the significance of these leukocytes in the diagnosis of MF has been reduced considerably by a study recently completed by McNutt and Crain.* They quantified the degree of nuclear irregularity in cells from the skin of 16 patients with MF and in cells from more than 100 patients with other diseases. By measuring the length of the nuclear membrane and by dividing this value by the square root of the cross-sectional area, they computed a nuclear contour index (NCI) and compared this value in the 2 groups of patients. The mean NCI was 6.1 in patients with MF and 4.6 to 5.4 in patients with other diseases. By setting the limit at an NCI of ≥ 6.1 and by requiring that $\geq 6\%$ of the lymphocytes have NCI ≥ 9, they obtained a false-positive rate of only 1%. No cell with an NCI as high as 16

* McNutt NS, Crain WR, unpublished data.

was found in any benign infiltrate (Figure 1), but such cells were seen in some of the skin samples from patients with MF. This work confirmed the impressions of past workers that cells with extremely irregular nuclear shapes were pathognomonic of MF and that the whole population of lymphocytes in the skin of MF patients had nuclei with abnormally irregular contours.

ABNORMAL CELL FUNCTIONING

Research next turned to elucidation of membrane and nuclear characteristics of the cells in MF. The seminal observation was published in 1971 when Crossen and co-workers [22] studied abnormal-appearing leukocytes from the blood of a patient with Sézary syndrome. They noted that the Sézary cells responded to phytohemagglutinin and concluded that the cells were of the lymphocytic series. Their conclusion was not original, but it did represent the 1st time that nonmorphological evidence had been presented to support the conclusion. Within the next 3 yr, groups in New York [23], Paris [24], and Bethesda [25] demonstrated that the abnormal cells had the membrane characteristics of thymus-derived cells and could form sheep erythrocyte rosettes. Electron microscopic study of the cells at the center of such rosettes confirmed that the cerebriform cells described by Lutzner and co-workers were indeed T cells. Circulating cells in patients with Sézary syndrome or cells teased from skin tumors [26] shared these characteristics. More recently, antibodies to human T cell antigen were used to show the distribution of the cells within tissue sections [27], and the cells in Pautrier abscesses as well as the dermis carried this antigen. Furthermore, in an *in vitro* system, circulating cells from 5 of 12 patients with Sézary syndrome stimulated normal B cells to produce immunoglobulin and thus served as helper T cells [28]; cells of the other 7 patients were presumably less well differentiated and did not retain this capacity.

CHROMOSOME ABNORMALITIES

Crossen and associates [22] examined the karotypes of the Sézary cells that phytohemagglutinin stimulated to divide and found definite aneuploidy. Their observation has been confirmed by several investigators; it is clear that chromosomal abnormalities occur in skin, lymph nodes, peripheral blood leukocytes, and even occasionally in bone marrow. These are more common when there are histologically abnormal cells at these sites, but they can be found even when such abnormalities are not detectable by light microscopy [29]. No single chromosomal abnormality seems to be characteristic of MF or the Sézary syndrome. Van Vloten, Van Duijn, and Schaberg [30] have used the finding of abnormal complement of chromosomes to improve diagnostic acumen beyond that attainable by light microscopy. They measured the DNA content of cells from patients with MF and Sézary syndrome as well as from patients only suspected of having MF but in whom routine light microscopic examination was not definitive. They predicted accurately which of the patients suspected of having MF would subsequently show histologically typical MF. In addition, they used this technique to separate patients with dermatopathic lymphadenopathy into 2 groups with markedly different prognoses. Van Vloten, Schaberg, and Van der Ploeg observed that cells from skin lesions of 5 patients with lymphomatoid papulosis had markedly abnormal DNA contents even though the lesions continued to involute spontaneously [31].

Thus, in one decade we have passed from a time when the existence of MF was seriously questioned to a time when there is widespread agreement about the general outlines of the clinical course and that the disease is a malignancy of helper T cells with an abnormal chromosomal complement diagnosable by techniques other than traditional light microscopy.

The sites of production of these cells, however, have not been proved. Clinicians see a disease that appears to be strictly cutaneous for years, and topical chemotherapy or electron beam irradiation limited to the skin can produce prolonged remission and perhaps even cures [5]; these facts favor the view that the abnormal cells multiply in the skin itself. However, areas of skin involvement are not contiguous, and therefore the disease must be multifocal, or the cells must have some early ability to migrate, probably through the bloodstream, to new skin sites. There are reports of circulating tumor cells in patients with disease otherwise apparently limited to cutaneous plaques [32], an indication that dissemination occurs via the bloodstream. It may be that in early stages of the disease the cells have such an affinity for skin that the overwhelming majority of them reside in it, where repeated doses of cytotoxic chemicals or irradiation can kill them, and that the repetition of such regimens eliminates the circulating cells when they return to the skin. Such a migration between skin and blood, of course, was suggested most elegantly by the successful management, through leukapheresis, of skin lesions in a patient with a high-count Sézary syndrome [33]. However, preliminary studies in which ^{3}H-thymidine was injected into patients with advanced disease suggested that although malignant cells in the skin can divide and those in the blood cannot, the bulk of circulating Sézary cells are produced extracutaneously [34].

SUMMARY

I have tried to present an overview of MF and to emphasize some of its clinical aspects, including the generally prolonged course with an infiltrate that is both clinically and histologically banal initially but that becomes obviously malignant eventually. Just as multifocal eosinophilic granuloma may be a proliferation of 1 type of nonkeratinocyte epidermal cell—the Langerhans cell—so MF may be a proliferation of a different type of nonkeratinocyte epidermal cell—a specialized T lymphocyte that is a normal component of skin-associated lymphoid tissue [35].

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